AD_____

AWARD NUMBER: W81XWH-04-1-0490

TITLE: Polychlorinated Biphenyls, Organochlorines & PD Risk: A Case Control Study in Alaska

PRINCIPAL INVESTIGATOR: Caroline M. Tanner, M.D., Ph.D.

CONTRACTING ORGANIZATION: Parkinson's Institute
Sunnyvale, CA 94089-1605

REPORT DATE: May 2008

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-05-2008	Annual	1 Apr 2007 – 31 Mar 2008

4. TITLE AND SUBTITLE

Polychlorinated Biphenyls, Organochlorines & PD Risk: A Case Control Study in Alaska

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-04-1-0490

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Parkinson's Institute
Sunnyvale, California 94089-1605

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The intent of this proposal is to conduct a case-control study of Parkinson's disease (PD) among Alaska Natives to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interview, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project is being conducted in two phases. Phase 1 is a developmental period and is complete for study conduct in Anchorage. The specific aspects of the study design were established, detailed protocols were developed, and the necessary Institutional Review Board (IRB) approvals for the research were obtained. Further approval is required for conduct outside of Anchorage. Phase 2, conduct of the case-control study, is now in progress in Anchorage.

15. SUBJECT TERMS
Parkinson's disease, polychlorinated biphenyl, organochlorine pesticides, methylmercury, Alaska natives, neurodegeneration

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	14	19b. TELEPHONE NUMBER *(include area code)*

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A. Introduction

The intent of this proposal is to conduct a case control study of Parkinson's disease (PD) among Alaska Native people to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides, and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interviews, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project is being conducted in two phases. Phase 1 was a developmental period and is complete for study conduct in Anchorage. The specific aspects of the study design were established, detailed protocols were developed, and the necessary Institutional Review Board (IRB) approvals for the research were obtained. Phase 2, conduct of the case-control study, is now in progress.

B. Body

SCOPE OF WORK - PHASE 1

Task 1: Develop an ascertainment protocol using Indian Health Service (IHS) provider databases as the primary source, and identifying other possible sources of cases.
Task 2: Develop methods for identifying matched controls.
Accomplishments:
Since the last reporting period, study personnel traveled to AK to meet with collaborating neurologists and representatives of the AK Area Institutional Review Board (IRB) to refine case and control ascertainment methods. These methods have been approved for use at the Alaska Native Medical Center (ANMC) in Anchorage.

Task 3: Develop a preliminary proposal for review by Alaska Native leaders. Subsequent detailed versions of the study protocol will be submitted for review in accordance with protocol.
Accomplishments:
The study protocol, data collection instruments, and informed consents were submitted and approved by all necessary regulatory boards and the Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) for study conduct at ANMC.

Task 4: Establishing appropriate infrastructure and personnel in Alaska. This will include a physician/neurologist, project manager, and local contacts within each tribal group. In addition, preliminary training in epidemiologic research methods may be a necessary part of a feasibility assessment.
Accomplishments:
Dr. Trimble, our local neurologist, has been involved with the project since its inception. In April 2007 we hired an Alaska based project manager, Amy Wiita. She completed human subjects training. She also completed training in study specific data collection methods.

Additionally, we established a comprehensive list of contacts within each tribal group.

Task 5: Develop study instruments and a detailed protocol.
Accomplishments:
Drafts were completed during year 2. We developed a study protocol and study instruments for collecting detailed life histories with special focus on exposures through diet, place of residence, and occupational exposures. After receiving approval from all review boards, the ORP USAMRMC requested additional changes to the protocol. Those changes were implemented, resubmitted, and approved since the last reporting period.

Task 6: Refining the study protocol and preparing the operations manual.
Accomplishments:
The study protocol was refined and approved for use in Anchorage. The operations manual has been drafted. This manual will continue to be updated as appropriate.

Task 7: IRB approval of final protocols.
Accomplishments:
IRB approval to recruit in the ANMC in Anchorage was achieved during this funding period, and the study has been initiated in Anchorage (see Table 1). There were many unexpected delays in achieving approval to conduct this work. The process required review by multiple human subjects committees prior to submission to the ORP USAMRMC. We received approval from all institutional review boards in 2007 and submitted the study protocol and materials for review by the ORP USAMRMC. The ORP USAMRMC requested changes to the protocol and consent forms. We implemented those changes, resubmitted these revised documents to the other institutional review boards and to the ORP USAMRMC. We received final documentation of approval to begin recruiting at the ANMC in Anchorage January 16, 2008 from the Alaska Area IRB.

As the study expands to other regions of Alaska, we will seek approval by native health corporations in those regions. Submissions to regional corporations are currently pending. We decided to wait until the study was initiated in Anchorage and data collection was well under way before going forward with regional submissions.

Table 1. Human Subject Approval Status

Institution	Review Board	Status	Expiration Date
Parkinson's Institute	WIRB	Approved	7/31/2008
ANMC	AK Area IRB	Approved	11/20/2008
ANMC	ANTHC - Board of Directors	Approved	NA*
ANMC	SCF	Approved	NA**
AK Statewide (Outside Anchorage basin)	Native Corporations as necessary	Submission pending	pending
PHRI	VA Pacific Islands Health Care System	Approved	10/1/2008
UCSF	UCSF Committee on Human Research	Approved	8/1/2008
USAMRMC	Office of Research Protections	Approved	10/16/2008

ANMC Alaska Native Medical Center
PHRI Pacific Health Research Institute
UCSF University of California San Francisco
WIRB Western Institutional Review Board
SCF SouthCentral Foundation
*Not applicable ANTHC defers all future review to the AAIRB
**Not applicable SCF does not administer an expiration date to their approval

SCOPE OF WORK - PHASE 2

Phase 2 was initiated in February 2008.
The goals of this phase are:

Task1: Identify approximately 50 cases of PD and 150 age matched participants without PD among the Native population in Alaska. This will be accomplished by working through tribal leaders, local health care providers and local contacts at the IHS to assist with identifying the most efficient and appropriate means of identifying cases and controls. Specifically, we will request assistance with gaining access to the IHS computerized medical record, the IHS hospital discharge data system, and pharmacy databases. These databases will be used to identify individuals with a diagnosis of PD and individuals on PD medications. Potential participants will be contacted by phone and administered a PD screening instrument. Those who agree to participate and who screen positively will be examined by a trained physician who will use standardized instruments for assessing Parkinson's disease (Unified Parkinson's Disease Rating Scale, Hoehn and Yahr stage, etc.). Participants will be videotaped to allow expert confirmation of diagnosis. Control participants will be selected from the same population and similarly screened.

Accomplished:

Cases: We established list of 10 International Classification of Disease (ICD-9) codes related to PD. The patient database at the ANMC was electronically searched for these 10 codes. The electronic output from this search was then compared to additional information provided by the local neurologist and case manager. To date, we have generated a list of 77 potential cases of interest statewide.

- 10 potential cases were screened at ANMC
  - 2 have enrollment in-progress
  - 7 provided informed consent and enrolled in the study
    - 1 finished all parts of the study
    - 6 have evaluations and interviews in-progress
  - 1 refused participation

Controls: At the ANMC, we worked with staff to establish an efficient means of control recruitment. We currently recruit in common areas of the ANMC using approved pamphlets, posters, and information sheets.

- 16 potential controls were screened at ANMC
  - 8 have enrollment in-progress
  - 8 provided informed consent and enrolled in the study
    - 8 finished all parts of the study
    - 0 have evaluations and interviews in-progress
  - 0 refused participation

Task 2: Draw blood from cases and controls to measure levels of PCBs, organochlorine pesticides and methyl mercury.

Accomplished:

Training was conducted to ensure the proper collection, shipment, and processing of blood samples. We established a network of ANMC clinic phlebotomists to be on-call for study blood draws. After labeling, the blood samples are shipped overnight to the Parkinson's Institute laboratory for processing and storage. To date, samples from 14 subjects have been collected, shipped, and processed.

Task 3: Administer a structured interview to cases and controls to identify information important to the characterization of PCB, organochlorine pesticides and methyl mercury exposure (life time diet, occupation, place of residence, recreational activities) or identifying potential confounders (smoking cigarettes, drinking coffee, alcohol).
Accomplished:
Of the 15 subjects enrolled, 9 interviews have been completed and 8 are in-progress.

Task 4. Estimate logistic regression models adjusted for age and other potential confounders to determine the odds of PD among those with high levels of PCB , organochlorine pesticides and methyl mercury exposure, individually and in combination, relative to the odds of PD among those with no or low levels of exposure the toxicants.
Accomplished:
This step will not be initiated until all data collection is complete.

C. Key Research Accomplishments

- Met with collaborating neurologists in AK and other local investigators to refine methods of case and control ascertainment.
- Revisions were made to study instruments, consents, and protocols to satisfy the requests of reviewers.
- Additional human subjects approval was obtained by all of the required review boards (see Table 1).
- Subject ascertainment, enrollment and data collection were initiated at the ANMC.

D. Reportable Outcomes

We will not have reportable outcomes until all data collection is finished statewide.

E. Conclusions

Following the completion of subject enrollment, data and sample collection, and analysis, it will be possible to draw relevant scientific conclusions.

F. References
None

G. Appendices
None

WIRB®
(360) 252-2500
1-800-562-4789
FAX: (360) 252-2498

Western Institutional Review Board ®

Western International Review Board®

3535 SEVENTH AVENUE, SW, OLYMPIA, WA 98502-5010
P.O. BOX 12029, OLYMPIA, WA 98508-2029

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Caroline M. Tanner M.D., Ph.D.
1170 Morse Avenue
Sunnyvale, California 94089-1605

BOARD ACTION DATED: 07/16/2007
PANEL: 7
STUDY APPROVAL EXPIRES: 07/31/2008
STUDY NUM: 1060268
WIRB PRO NUM: 20041208
INVEST NUM: 8644
WO NUM: 1-438476-1
CONTINUING REVIEW: Annually
SITE STATUS REPORTING: Annually

SPONSOR: US Army Medical Research Acquisitions Activity
PROTOCOL NUM: W23RYX-4007-N601
AMD. PRO. NUM:
TITLE:
Polychlorinated Biphenyls, Organochiorines and Parkinson's Disease Risk A Case Control Study in Alaska Natives

APPROVAL INCLUDES:

Study and Investigator for an additional continuing review period. This approval expires on the date noted above.

WIRB APPROVAL IS GRANTED SUBJECT TO:

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789
This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Full AAHRPP Accreditation

Theodore D. Schultz, J.D., Chairman

7/23/2007
(Date)

This document electronically reviewed and approved by Schultz, Ted on 7/23/2007 10:50:18 AM PST. For more information call Client Services at 1-360-252-2500

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate.

    a. Use only the most current consent form bearing the WIRB "APPROVED" stamp.

    b. Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB.

    c. Obtain pre-approval from WIRB for use of recruitment materials and other materials provided to subjects.

3. Obtain pre-approval from WIRB for any planned deviations that could adversely affect the safety or welfare of subjects, or the integrity of the research data and any changes in the research activity. The only exception is when changes are necessary to eliminate apparent immediate hazards to subjects. Immediately report to WIRB any such emergency changes implemented.

4. Promptly report to WIRB any new information that may adversely affect the safety of the subjects or the conduct of the trial.

    a. Report to WIRB all adverse events that are unanticipated and possibly related, within 10 days of the investigator becoming aware of them.

    b. Promptly report to WIRB other unanticipated problems involving risks to human subjects or others. These events do not readily fit the formal definition of Adverse Event, but could impact human subject safety and/or rights. Examples include theft of a computer containing private identifiable subject information, or study staff getting ill from inhaling a study agent.

    c. Provide reports to WIRB concerning the progress of the research, when requested.

5. Report to WIRB any unplanned protocol variance that could adversely affect the safety or welfare of subjects, or the integrity of the research data, within 10 days of becoming aware of the variance. Other unplanned variances may be recorded on a log and submitted with continuing review reports.

Federal regulations require that WIRB conduct continuing review of approved research. You will receive Continuing Review Report forms from WIRB. These reports must be returned even though your study may not have started.

DISTRIBUTION OF COPIES:

Contact	**Company Name**
Caroline M. Tanner M.D., Ph.D.	The Parkinson's Institute
Monica Korell	The Parkinson's Institute

SITES: If the PI has an obligation to use another IRB for any site listed below and has not submitted a written statement from the other IRB acknowledging WIRB's review of this research, please contact WIRB's Client Services department.

Address
1170 Morse Avenue, Sunnyvale, California 94089-1605

December 18, 2007

Brian Trimble, MD
Caroline Tanner, MD, PhD
Alaska Native Medical Center, Internal Medicine
4315 Diplomacy Drive
Anchorage, Alaska 99508

Dear Dr. Tanner and Dr. Trimble;
During the November 20, 2007 meeting of the Alaska Area IRB the committee reviewed the protocol and all accompanying documents of the project titled: **2005-04-005 Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk : A Case Control Study in Alaska Natives.** The Alaska Area Institutional Review Board (AAIRB) has given approval for the protocol to continue. Tribal approval must be obtained in addition to the IRB approval.

The Alaska Area IRB (AAIRB) has given approval for the protocol with an expiration date of **November 20, 2008**. As a reminder, the protocol and all accompanying documents **may not have modifications** for this decision to remain valid. It is your responsibility as Principal Investigator (PI) to maintain the status of your project by tracking, and monitoring all activities related to the protocol.
All research approved by the Alaska Area IRB is subject to 45 CFR 46 "Protection of Human Subjects" regulations and the principles of the Belmont Report. Investigators are expected to be familiar with these provisions and adhere strictly to all requirements. You are required to have all personnel involved in the research complete the training at www.citiprogram.org, once every 36 months. Please retain your completion certificates from the Collaborative IRB Training Institute (CITI).

Prior to making any changes to the protocol you must receive approval from the Alaska Area IRB. Please request our Status Report and Renewal Application forms from the IRB Administrator at least 6 weeks prior to the protocol expiration date. Please ensure that project renewal information is complete and submitted to the IRB Administrator at least four weeks prior to expiration. The continuing review information should include but not be limited to the Alaska Area IRB Status report and renewal application form, a current copy of the consent/assent forms, a cover letter to the IRB with a project summary and an electronic copy of all items to be sent to the IRB members. The submission date for the monthly IRB meeting is the first day of each month. Please inform the IRB by letter when the protocol is complete/closed.

As a reminder, the IRB must review and approve all human subjects' research protocols at intervals appropriate to the degree of risk, but not less than once per year. Per 45 CFR 46.109(e), there is no grace period beyond one year from the last IRB approval date unless the protocol approval period is shorter than one year.

It is your responsibility as Principal Investigator (PI) to maintain the approval status for your project by tracking, renewing and obtaining IRB approval for all modifications to the protocol and the consent form. Please keep this approval in your protocol file as proof of IRB approval and as a reminder of the expiration date. To avoid lapses in approval of your research which will result in suspension of participant enrollment and/or termination of the protocol submit the protocol continuation request at least 4 weeks prior to **expiration date of November 20, 2008.**

This IRB action does not constitute review or compliance with HIPAA requirements. Prior to access and/or use of data, you must receive approval from the appropriate institutional officials releasing this information under the current HIPAA requirements.

All research involving staff, patients or resources at the Alaska Native Medical Center (ANMC) must be submitted to the Board(s) of Directors of ANMC's parent organizations after Alaska Area Institutional Review Board approval is obtained. The parent organizations of ANMC are the Southcentral Foundation (SCF) and the Alaska Native Tribal Health Consortium (ANTHC). Your point of contact at ANTHC is Kathy Koller, RN, MSN at kkoller@anmc.org. Your point of contact at SCF is Dr. Ruth Etzel at raetzel@southcentralfoundation.com. Please send a copy of your approved research protocol and a copy of the Alaska Area IRB approval letter to each of them. In addition all research protocols must receive tribal approval.

If this protocol utilizes information from the Alaska Native Medical Center you must submit any manuscripts, reports, or abstracts for consideration for publication or presentation to the Abstracts Manuscripts and Publications Committee (AMP RC) for review. In addition the ANTHC and SCF Board of Directors approval must be obtained. To ensure timely review, please send an electronic copy of these items to both Dr. Etzel and Mrs. Koller at least 8 weeks before the deadline for submission.

If you have further questions for the Alaska Area IRB you may contact me at tjpowell@anmc.org or call (907) 729-3924 between the hours of 8:00am and 4:00pm, Monday through Thursday.

Sincerely,

Terry J. M. Powell
IRB Administrator
Alaska Area Institutional Review Board
4315 Diplomacy Drive RMCC
Anchorage, Alaska 99508

COMMITTEE ON HUMAN RESEARCH
OFFICE OF RESEARCH, Box 0962
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
www.research.ucsf.edu/chr/Apply/chrApprovalCond.asp
chr@ucsf.edu
(415) 476-1814

CHR APPROVAL LETTER

TO: Marion M. Lee, Ph.D.
Box 0981

RE: Polychlorinated Biphenlys, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Native People

The Committee on Human Research (CHR) has reviewed and approved this application to involve humans as research subjects. This included a review of all documents attached to the original copy of this letter.

The CHR is the Institutional Review Board (IRB) for UCSF and its affiliates. UCSF holds Office of Human Research Protections Federalwide Assurance number FWA00000068. See the CHR website for a list of other applicable FWA's.

APPROVAL NUMBER: H6442-25720-04. This number is a UCSF CHR number and should be used on all correspondence, consent forms and patient charts as appropriate.

APPROVAL DATE: August 1, 2007 **EXPIRATION DATE:** August 1, 2008 **Expedited Review**

GENERAL CONDITIONS OF APPROVAL: Please refer to www.research.ucsf.edu/chr/Apply/chrApprovalCond.asp for a description of the general conditions of CHR approval. In particular, the study must be renewed by the expiration date if work is to continue. Also, prior CHR approval is required before implementing any changes in the consent documents or any changes in the protocol unless those changes are required urgently for the safety of the subjects.

HIPAA "Privacy Rule" (45CFR164): This study does not involve access to, or creation or disclosure of Protected Health Information (PHI).

Sincerely,

Susan H. Sniderman, M.D.
Chair, Committee on Human Research

cc:

DEPARTMENT OF VETERANS AFFAIRS
VA PACIFIC ISLANDS HEALTH CARE SYSTEM
Spark M. Matsunaga Medical Center
459 Patterson Road
Honolulu HI 96819-1522

October 2, 2007

In Reply Refer To: 151/RCC

G. Webster Ross, MD
PHRI
846 S. Hotel Street, Suite 306
Honolulu, HI 96813

SUBJ: Project Number: 2002006-01/GWR/PROMISE 0013
Project Title: "Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Native People"

Dear Dr. Ross:

I am pleased to inform you that on October 2, 2007 the VAMC Research & Development (R&D) Committee (RDC) reviewed and unanimously approved your Annual Project Update, until September 30, 2008 (leap year), for the project cited above.

The RDC concurred with the September 13, 2007 Institutional Review Board (IRB) evaluation and determination of level of human subject risk as "minimal". The RDC also concurred with the IRB approval of continued human subject use for a period of one-year and their determination that your approved waivers of informed consent and HIPAA authorization remain valid..

Your next Annual Project Update must be completed prior to October 1, 2008. The Annual Update must be filed with the R&D Office at least one month prior to the September 2008 meeting. The R&D Committee is normally held on the first Tuesday of each month; however, the schedule can change depending on availability of members. Please check with the R&D Office in advance for final schedule.

If you have any questions, please contact Douglas Miller, Research Committee Coordinator at (808) 433-0127 or e-mail: douglas.miller@va.gov.

Sincerely,

H. Stefan Bracha, MD
Deputy Chairperson, R&D Committee